



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|--|
| (51) International Patent Classification ⁶: C07C 229/22, 271/22, 275/16, C07D 257/04, C07F 9/54, 9/6561, A61K 31/195, 31/41, 31/66 | A1 | (11) International Publication Number: WO 99/59957 (43) International Publication Date: 25 November 1999 (25.11.99) |
| (21) International Application Number: PCT/IT99/00126 (22) International Filing Date: 11 May 1999 (11.05.99) (30) Priority Data: MI98A001075 15 May 1998 (15.05.98) IT (71) Applicant (for all designated States except US): SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.p.A. [IT/IT]; Viale Shakespeare, 47, I-00144 Rome (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): GIANNESI, Fabio [IT/IT]; Via Berlinguer, 7, I-00040 Pomezia (IT). MARZI, Mauro [IT/IT]; Via Antonio Ciamarra, 158, I-00169 Rome (IT). MINETTI, Patrizia [IT/IT]; Via Nanchino, 28, I-00144 Rome (IT). DE ANGELIS, Francesco [IT/IT]; Piazza A. Friggeri, 13, I-00136 Rome (IT). TINTI, Maria, Omella [IT/IT]; Via Ernesto Basile, 81, I-00182 Rome (IT). CHIODI, Piero [IT/IT]; Via Trento, 3, I-00043 Ciampino (IT). ARDUINI, Arduino [IT/IT]; Via della Camilluccia, 701, I-00135 Rome (IT). | | (74) Agent: SPADARO, Marco; Sigma-Tau Industrie Farmaceutiche Riunite S.p.A., Viale Shakespeare, 47, I-00144 Rome (IT). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: COMPOUNDS HAVING REVERSIBLE INHIBITING ACTIVITY OF CARNITINE PALMITOYL-TRANSFERASE <div style="text-align: center;"> $\text{X}^+ - \text{CH}_2 - \underset{\substack{ \\ \text{Z}}}{\text{CH}} - \text{CH}_2 - \text{Y}^- \quad (I)$ </div> (57) Abstract <p>Compounds of formula (I) wherein the groups are as defined in the description are disclosed. The compounds of formula (I) are endowed with reversible inhibiting activity of carnitine palmitoyl-transferase and are useful in the preparation of medicaments useful in the pathologies related to a hyperactivity of carnitine palmitoyl-transferase, such as hyperglycemia, diabetes and pathologies related thereto, heart failure, ischemia.</p> | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 99/00126

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C229/22 C07C271/22 C07C275/16 C07D257/04 C07F9/54
C07F9/6561 A61K31/195 A61K31/41 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 93 25197 A (AFFYMAX TECHNOLOGIES) 23 December 1993 (1993-12-23) page 135, line 35 - page 136, line 21 --- | 1,2 |
| X | ZHI-HENG HUANG ET AL.: "Analysis of Acylcarnitines as Their N-Demethylated Ester Derivatives by Gas Chromatography-Chemical Ionization Mass Spectrometry" ANALYTICAL BIOCHEMISTRY., vol. 199, no. 1, 15 November 1991 (1991-11-15), pages 98-105, XP002115164 ACADEMIC PRESS INC. NEW YORK., US ISSN: 0003-2697 page 99, scheme 1; page 102, figure 7 --- -/- | 1,2 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

13 September 1999

Date of mailing of the international search report

28/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 99/00126

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 98 00389 A (SANG JEW ET AL.) 8 January 1998 (1998-01-08) page 1 - page 2; claims --- | 1,13 |
| A | US 5 196 418 A (RICHARD D. GANDOUR ET AL.) 23 March 1993 (1993-03-23) claims --- | 1,13 |
| A | EP 0 574 355 A (SANDOZ) 15 December 1993 (1993-12-15) cited in the application claims --- | 1,13 |
| A | WO 85 04396 A (CORNELL RESEARCH FOUNDATION) 10 October 1985 (1985-10-10) cited in the application claims ----- | 1,13 |

INTERNATIONAL SEARCH REPORT

national application No.

PCT/IT 99/00126

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19,22,26 and 27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19,22,26 and 27
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IT 99/00126

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|--|--|
| WO 9325197 A | 23-12-1993 | AU 4534593 A EP 0647133 A US 5814603 A US 5622944 A US 5607691 A AU 6764794 A CA 2153243 A EP 0683668 A JP 8510720 T WO 9417792 A | 04-01-1994 12-04-1995 29-09-1998 22-04-1997 04-03-1997 29-08-1994 18-08-1994 29-11-1995 12-11-1996 18-08-1994 |
| WO 9800389 A | 08-01-1998 | AU 3464497 A | 21-01-1998 |
| US 5196418 A | 23-03-1993 | NONE | |
| EP 574355 A | 15-12-1993 | AT 156828 T AU 667537 B CA 2098133 A CN 1086217 A, B CZ 9301083 A DE 69313029 D DE 69313029 T DK 574355 T ES 2105194 T FI 932662 A GR 3024684 T HU 65327 A HU 9500248 A IL 105965 A JP 6073077 A NO 932096 A NZ 247840 A SG 42983 A SK 58893 A US 5516767 A ZA 9304157 A | 15-08-1997 28-03-1996 12-12-1993 04-05-1994 15-02-1995 18-09-1997 29-01-1998 26-01-1998 16-10-1997 12-12-1993 31-12-1997 02-05-1994 28-11-1995 18-03-1997 15-03-1994 13-12-1993 27-04-1995 17-10-1997 08-06-1994 14-05-1996 05-09-1994 |
| WO 8504396 A | 10-10-1985 | AT 48832 T AU 570112 B AU 4216685 A CA 1297901 A EP 0177574 A JP 6062523 B JP 61501776 T US 4781863 A | 15-01-1990 03-03-1988 01-11-1985 24-03-1992 16-04-1986 17-08-1994 21-08-1986 01-11-1988 |